Prostate Cancer Screening and Surgical Management

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Objectives

- Update the latest prostate cancer statistics
- Review Diagnosis and Staging
- Review data concerning PSA screening:
  - PLCO
  - ERSPC
- Latest AUA Recommendations
- Treatment Options
Epidemiology

- Prostate cancer is a global problem
- Today we focus on the debate of prostate cancer in the US and Europe
- We often overlook the fact that prostate cancer is really a global phenomenon
- Some of the highest mortality rates found in the least developed regions of the world: Caribbean, South America, and Africa

Epidemiology

- Prostate cancer is the most common
- 116,360 cases
- 26,150 deaths
- Now third leading cause of cancer deaths (lung and colon kill more men)
**Epidemiology**

- Prostate cancer projections, 2017
  - Highest incidence among men
  - Third leading cause of cancer death in men (down from #2)

- Nevertheless, the number of men diagnosed is decreasing, compared to the 1990s

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**Epidemiology**

- Mortality rates are declining in the PSA era
  - APC -3.4% (2005-2014)
  - 10,000 lives saved
Early Detection

- Best prognosis follows early detection
- Recent data on lower mortality rates of prostate cancer
- Affords patients many options for treatment

Early Detection

- Digital Rectal Exam (DRE)
- Prostate Specific Antigen (PSA) blood test
- Any abnormality in the PSA or DRE will require
  - Biopsy of the prostate
    - Ultrasound guided
    - Usually performed in the office
    - Short procedure
Biopsy Results

- Prostate cancer graded on appearance of cancer cells
- Gleason grading system
  - Gleason grade ranges from 1 (least aggressive) to 5 (most aggressive)
- Gleason score (2-10)
  - Most common cell grade (first) added to second most common cell grade, e.g., Gleason 7 (3+4)

**Gleason Grading**

<table>
<thead>
<tr>
<th>Least aggressive</th>
<th>Most aggressive</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2** The update to the Gleason scoring system

<table>
<thead>
<tr>
<th>Traditional Gleason score</th>
<th>New ISUP score</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>3 + 4 = 7</td>
<td>2</td>
</tr>
<tr>
<td>4 + 3 = 7</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>9 – 10</td>
<td>5</td>
</tr>
</tbody>
</table>

ISUP, International Society of Urological Pathology.
Staging of Prostate Cancer

- PSA
- Digital Rectal Exam
- Trans Rectal Ultrasound
- Gleason Score
- Bone Scan
- +/- CT scan or MRI
- Biopsy and TNM staging system
  - Tumor, Nodes, Metastases

Prostate Cancer T1 Disease

- Tumor cannot be felt
- T1a – cancer found in ≤ 5% TURP specimen
- T1b - cancer found in ≥ 5% TURP specimen
- T1c – cancer found as a result of PSA elevation only
Prostate Cancer T2

- Tumor can be felt during DRE (digital rectal exam)
- T2a – felt on ≤ one half of one side of prostate
- T2b – felt on ≥ one half of both sides of prostate
- T2c – felt on both sides of prostate

Prostate Cancer T3

- Cancer has spread beyond the prostate
- T3a – extra capsular extension
- T3b – tumor invades seminal vesicle(s)
Prostate Cancer T4

- Cancer has invaded local organs/tissues
  - Bladder muscle
  - Pelvic side wall
- May cause pain in joints and back
But, a fact: SEER, 2015
RCT’s Prostate Cancer Screening

Two studies:
US – PLCO. Rigorous. Conducted in US

*Problem: PSA testing had already taken off like wildfire in the U.S.*

Europe – ERSPC – PSA testing. *Advantage: little background PSA testing.*

*Problem: almost a meta-analysis of several different trials.*
Screening Trials

Prostate Cancer Screening in the Randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: Mortality Results after 13 Years of Follow-up

Mortality results from the Göteborg randomised population-based prostate-cancer screening trial

The PLCO Clinical Trial

METHODS

From 1993 through 2001, we randomly assigned 76,693 men at 10 U.S. study centers to receive either annual screening (38,343 subjects) or usual care as the control (38,350 subjects). Men in the screening group were offered annual PSA testing for 6 years and digital rectal examination for 4 years. The subjects and health care providers received the results and decided on the type of follow-up evaluation. Usual care sometimes included screening, as some organizations have recommended. The numbers of all cancers and deaths and causes of death were ascertained.
PLCO Design

- 1993-2001
- 77,000 men randomized to annual screening for 6 years vs. “usual care”
- Men w/ PSA WNL prior to enrollment included
- Men w/ elevated PSA prior to enrollment excluded

PLCO: More cancers detected

PLCO: No reduction in deaths


**PLCO Summary**

**Criticisms**
- Changing definition of “usual care” in the 1990s
- 44% of participants had >/ 1 PSA prior to enrollment
- 90% contamination of “usual care” group
  - Shoag, Mittal NEJM 2016
- Biopsy rates for elevated PSA only 30-40%

**Conclusions**
- PLCO is not “screening vs. no screening”
- More accurate: “annual vs. opportunistic” screening
- PLCO should not be included in analysis of screening trials
- PLCO is not evidence that screening doesn’t improve PCSM
ERSPC Design

- 1991-2003
- 182,000 men randomized
- Majority screened every 4 years
- Majority biopsied for PSA > /4
- Less contamination, larger risk profile differences between groups
**ERSPC Results**

- At 9 years, 21% relative risk reduction in PCSM
- After adjustment for contamination, even higher risk reduction (29%)
- NND = 37 at 11 years follow-up

![Graph showing cumulative hazard of death from prostate cancer among men 55 to 69 years of age.](image)

**ERSPC Summary**

<table>
<thead>
<tr>
<th>Criticisms</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• NND at 11 years follow up is still too short to be accurate</td>
<td>• ERSPC is an imperfect but valid study of prostate cancer screening</td>
</tr>
<tr>
<td>• Predictive models with 25 years follow up show NND = 2-9</td>
<td>• The true magnitude of screening benefit is unknown because of inadequate follow-up</td>
</tr>
</tbody>
</table>

*Figure 2. Cumulative Hazard of Death from Prostate Cancer among Men 55 to 69 Years of Age. Values are not included for centers in France because of the short follow-up period (median, 4.6 years). The Nelson−Aalen method was used to calculate the cumulative hazard of death from prostate cancer.*
Goteborg Design

- 1994-2008

- Nearly 20,000 men randomized to PSA screening every 2 years, or no screening until age 69

- Median age was 56: youngest of 3 major trials

Goteborg Results

- 14 years of follow-up

- 44% relative risk reduction in PCSM

- NND = 12

- Diverging survival curves at the end of follow-up period
Summary of RCTs in Prostate Cancer Screening

- Of the 3 major screening trials, only 2 are valid to answer the question
  - Conclusions from ERSPC and Goteborg are concordant

- Data from PLCO should not be included in the discussion
  - This is not controversial

- Bottom Line: PSA screening reduces prostate cancer specific mortality

May, 2012: USPSTF Recommendations

- Outcome:
  - The USPSTF recommends against PSA-based testing for prostate cancer (Grade “D”)

- Origin of Controversy
  - Underappreciation of benefit
    - Emphasis on PLCO and ERSPC trials
    - No extrapolation of ERSPC data via modeling for NND
    - Goteborg Trial ignored
May, 2012: USPSTF Recommendations

Origin of Controversy

Overestimation of Harms

➢ Emphasis on false positives
➢ Men prefer to be designated cancer free, even if negative biopsy required.

<table>
<thead>
<tr>
<th>Screening health state</th>
<th>Ranked as &quot;best&quot; state</th>
<th>Ranked as &quot;worst&quot; state</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>7 (4.2%)</td>
<td>146 (86.9%)</td>
</tr>
<tr>
<td>B</td>
<td>96 (57.1%)</td>
<td>3 (1.8%)</td>
</tr>
<tr>
<td>C</td>
<td>65 (38.7%)</td>
<td>19 (11.3%)</td>
</tr>
</tbody>
</table>

A = no cancer, no PSA test and no biopsy; B = no cancer and a favourable (negative) PSA test; C = no cancer, an unfavourable (positive) PSA test and a favourable (negative) biopsy.

May, 2012: USPSTF Recommendations

• Origin of Controversy
  • Overestimation of Harms
    • Focus on morbidity data from treatment of prostate cancer
      • Cites 0.5% complication rate from Medicare data in open prostatectomy era
      • More contemporary data shows lower morbidity rates (<0.1%)
May, 2012: USPSTF Recommendations

• Origin of Controversy
  • Overestimation of Harms
    • Ignores contemporary attitude that uncouples diagnosis from intervention
    • Men who enlist in active surveillance avoid operative morbidity

Impact of the USPSTF Recommendation

- Screening
- Biopsy
- Diagnosis
- Stage Migration
Impact of the USPSTF: Rates of screening across age groups - Survey Data

- Prostate cancer screening rates have declined since 2012
  - NHIS used to estimate screening rates based on 9-year mortality index for men >40
  - 2005, 2010, and 2013 compared
    - Age 50-59 rates 33→24% (p<0.01)
    - Age 60-74 rates 51→43% (p<0.01)
    - Age >75 rates 44→27% (p=0.03)

Fig 1. Proportion of men, by 5-year age group, who saw a physician in the year prior and received a prostate-specific antigen (PSA) test for screening purposes.

Impact of USPSTF: Rates of screening across age groups - Survey Data

- Prostate cancer screening rates have declined since 2012
  - NAMCS of primary care visits where DRE and PSA performed
  - DRE rates 65% decrease
  - PSA rates 39% decrease
Impact of USPSTF: Rates of screening across age groups- Claims/EMR data

- Prostate cancer screening rates have not declined since 2012
  
  - UTSW review of institutional PSA orders and urology referrals
  
  - The number of PSAs per ambulatory visit and urology referrals were unchanged

Impact of USPSTF: Rates of prostate biopsy

- Prostate biopsy rates have declined
  
  - Claims data from >5 million men with Medicare and private insurance
  
  - 2005-2014: 33% drop in prostate biopsies
  
  - 64 → 43 biopsies per 100,000 men
Impact of USPSTF: Rates of diagnosis-localized disease

Barocas et al, JUrol, 2015

- NCDB Analysis
- 2010-2012

<table>
<thead>
<tr>
<th>Group</th>
<th>Cancer type</th>
<th>Absolute Change</th>
<th>% Change</th>
<th>Absolute Change</th>
<th>% Change</th>
<th>Absolute Change</th>
<th>% Change</th>
<th>Absolute Change</th>
<th>% Change</th>
<th>Absolute Difference</th>
<th>% Difference</th>
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<tr>
<td>Prostate</td>
<td></td>
<td>39</td>
<td>0.4</td>
<td>-1,373</td>
<td>-12.2</td>
<td>-164</td>
<td>-1.8</td>
<td>-3,181</td>
<td>-27.9</td>
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<tr>
<td>Colon</td>
<td></td>
<td>3</td>
<td>0.1</td>
<td>4</td>
<td>0.2</td>
<td>-27</td>
<td>-0.5</td>
<td>-298</td>
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<tr>
<td>Prostate cancer subgroup:</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Low</td>
<td></td>
<td>9</td>
<td>0.3</td>
<td>-505</td>
<td>-16.9</td>
<td>-57</td>
<td>-2.7</td>
<td>-1,134</td>
<td>-37.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td>26</td>
<td>0.8</td>
<td>-437</td>
<td>-12.9</td>
<td>-50</td>
<td>-1.9</td>
<td>-1,080</td>
<td>-28.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td></td>
<td>4</td>
<td>0.1</td>
<td>-300</td>
<td>-10.1</td>
<td>-34</td>
<td>-1.4</td>
<td>-674</td>
<td>-23.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-localized</td>
<td></td>
<td>2</td>
<td>0.3</td>
<td>-14</td>
<td>-2.7</td>
<td>1</td>
<td>0.1</td>
<td>-6</td>
<td>-1.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Impact of USPSTF: Rates of diagnosis-localized disease

Barocas et al. JUrol, 2015

- NCDB Analysis
- 2010-2012
Impact of USPSTF: Rates of diagnosis-localized disease

Herget et al, JUrol, 2016

- SEER analysis
- 2007-2012
- Rate of decline by risk group
  - Low risk
    - 18% 2007-2008, then 29% after 2011
  - Intermediate risk
    - 8% 2007-2010, then 21% after 2011
  - High Risk
    - 2% 2007-2011, then 11% after 2011

Impact of the USPSTF: Reverse stage migration

- Statistical models exist to project effect of screening discontinuation
  - As high as 50% increase in metastatic cases at presentation
  - 20% increase in prostate cancer deaths

- Actual data to evaluate this is immature and inconclusive
Impact of the USPSTF: Summary

- The USPSTF recommendations had notable effects on screening/biopsy/diagnosis rates in a very short time period

AUA Guidelines Update 2013

- Meanwhile, the AUA released an updated guideline in 2013
- Represented a systematic review of the evidence by noted experts
- Emphasis on an individualized, risk adapted approach through shared decision making
AUA Guidelines: Statement 1

- The Panel recommends against PSA screening in men under age 40 years. (Recommendation; Evidence Strength Grade C)
  - In this age group there is a low prevalence of clinically detectable prostate cancer, no evidence demonstrating benefit of screening and likely the same harms of screening as in other age groups.

AUA Guidelines: Statement 2

- The Panel does not recommend routine screening in men between ages 40 to 54 years at average risk. (Recommendation; Evidence Strength Grade C)
  - For men younger than age 55 years at higher risk (e.g. positive family history or African American race), decisions regarding prostate cancer screening should be individualized.
AUA Guidelines: Statement 3

- For men ages 55 to 69 years the Panel strongly recommends shared decision-making for men age 55 to 69 years that are considering PSA screening, and proceeding based on a man's values and preferences. (Standard; Evidence Strength Grade B)
- The greatest benefit of screening appears to be in men ages 55 to 69 years.

AUA Guidelines: Statement 4

- To reduce the harms of screening, a routine screening interval of two years or more may be preferred over annual screening in those men who have participated in shared decision-making and decided on screening.
**AUA Guidelines: Statement 5**

- The Panel does not recommend routine PSA screening in men age 70+ years or any man with less than a 10 to 15 year life expectancy. (Recommendation; Evidence Strength Grade C)
  - Some men age 70+ years who are in excellent health may benefit from prostate cancer screening.

**Other agencies follow suit...**

- American College of Physicians, 2013
  - “ACP recommends that clinicians base the decision to screen for prostate cancer using the prostate-specific antigen test on the risk for prostate cancer, a discussion of the benefits and harms of screening, the patient’s general health and life expectancy, and patient preferences.”

  - “ACP recommends that clinicians should not screen for prostate cancer using the prostate-specific antigen test in average-risk men under the age of 50 years, men over the age of 69 years, or men with a life expectancy of less than 10 to 15 years.”
Update to USPSTF Recommendations

- May 8, 2017
  - USPSTF releases draft update upgrading screening recs for men 55-69 to grade “C”
  - For men >70, grade remained “D”.

“The decision about whether to be screened for prostate cancer should be an individual one. The USPSTF recommends individualized decision making about screening for prostate cancer after discussion with a clinician, so that each man has an opportunity to understand the potential benefits and harms of screening and to incorporate his values and preferences into his decision.”

Where does prostate cancer stand in 2018?

- We are at a cross-roads.
- Screening of healthy, young, well-informed men with serum PSA significantly reduces the risk of dying from prostate cancer (21-44%)
- However, does so at the risk of over-detection of low-grade tumors which would not have become clinically apparent over a patient’s lifetime if left untreated
- Although enthusiasm has grown for surveillance over-detection and over-treatment remain are tightly linked

Cancer Cases Control 19:175; NEJM 360:1320; Lancet Oncol 2010 11:725; NEJM 2011;364:1708
Cumulative prostate cancer mortality

Schroder et al., Lancet 2014
**ERSPC: Cumulative prostate cancer mortality**

Schroder et al., Lancet 2014

**Challenges: molecular and clinical heterogeneity**

- Substantial heterogeneity exists among primary prostate cancers
  - Clinically, Biologically
- Slow growing “indolent” → lethal malignancy
- Distinct molecular subtypes may underlie the highly varied clinical behavior
- **Need to develop single, widely accessible screening tests assess this complexity**

TCGA Network, Cell. 2015 Nov 5; 163(4): 1011-25
10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer

- 82,249 men screened with PSA aged 50-69 between 1999-2009
  - 2,664 diagnosed with PCa → 1,643 randomized
- Median f/u 10 years
- Three arms:
  1. “AS” (n=545);
  2. RP (n=553);
  3. RT (n=545)
- Primary Outcome: PCSM at median of 10 year f/u
- Secondary: disease progression, metastasis, ACS

Hamdy FC et al. NEJM, Sept 2016

How relatable was surveillance protocol?

- Some (9) with Gleason >6 (5 in AS)
- Surveillance protocol: PSA monitoring every 3 months in the first year and then every 6-12 months
- Increases of 50% over 12 months triggered review and potentially treatment
- Period biopsy not mandated
- **54.8% of patients initially enrolled in surveillance were treated**
ProtecT: Take Home Points

A Prostate-Cancer-Specific Survival

- Surgery
- Radiotherapy
- Active monitoring

No difference in 10-year mortality

p = 0.48

No. at Risk

<table>
<thead>
<tr>
<th>Year</th>
<th>1643</th>
<th>1628</th>
<th>1605</th>
<th>1575</th>
<th>1286</th>
<th>746</th>
</tr>
</thead>
</table>

Hamdy FC et al. NEJM, Sept 2016

B Freedom from Disease Progression

- Increased risk of progression and metastatic disease (~2-fold), (p = 0.004)

Could these have been detected earlier?

p < 0.01

No. at Risk

<table>
<thead>
<tr>
<th>Year</th>
<th>1643</th>
<th>1601</th>
<th>1533</th>
<th>1467</th>
<th>1175</th>
<th>666</th>
</tr>
</thead>
</table>

Hamdy FC et al. NEJM, Sept 2016
ProtecT: Take Home Points

• **At 10 year follow-up, mortality from low-risk prostate cancer is low, regardless of treatment assignment**
  - *Implications for who we screen and offer treatment*
• Definitive treatment associated with **lower** rates of disease progression and metastasis than active monitoring
• Surveillance protocol was largely PSA based which does not mirror contemporary standards
  - *We cannot freeze frame at diagnosis*
  - *Reinforces need to optimize protocols, tools, and endpoints*

Hamdy FC et al. NEJM, Sept 2016

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**We need to improve on current standard**

✓ PSA is an imperfect biomarker for prostate cancer
  - Incidental detection of indolent tumors threatens to erode early detection altogether!
✓ **Initial clinical risk stratification is inadequate and lead to over-treatment**
  - High reclassification rate
✓ Endpoints during surveillance may detect progression after it has occurred
Conclusions

- The inherent limitations of “standard” clinical tools including PSA are associated with unacceptably poor specificity for detecting high grade disease
- Undermine screening (USPSTF)
- An array of new biomarkers, and genomic assays have been validated predictors of numerous, actionable endpoints
  - **Aggressive disease at biopsy**
  - **Adverse pathology**
  - **Recurrence/metastasis/mortality after treatment**
- Preliminary data suggests that the use of these tools are effective in influencing behavior
- **Skepticism is good!**-- but we should not fear new tools!

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Can we refine biopsy selection using better markers?

- **Promise is held in the development and validation of novel biomarkers that possess greater specificity for high risk disease**
- **Many exist:** PCA3, TMPRSS2-ERG (MiPS), ExoDx
- Better selection for biopsy may reduce over-diagnosis
- **Prostate Health Index (PHI):** [-2]proPSA: splice-variant isoform of total PSA
  - AUC for detection of biopsy Gleason ≥3+4=0.707 among 658 men with PSA 4-10
- **4-Kallikrein Panel (4K):** Kallikrein-related peptidase 2 (hK2), intact PSA, free and total PSA
  - AUC for detection of biopsy Gleason ≥3+4=0.821 among 1,012 men with any total PSA

Detection of Gleason ≥3+4

- Overall AUC=0.707
- % free=0.661
- [-2]proPSA=0.558
- PSA=0.551

*PHI outperforms individual components

Loeb S et al. J Urol 2015

Have these markers been directly compared?

- Comparison of 531 men with PSA levels between 3-15 ng/mL undergoing first time biopsy 2010-2012
- **AUC for prediction of any grade and high grade (Gleason ≥3+4 PCa) not significantly different**
  - 4K: 0.69 (any grade); 0.718 (high grade)
  - PHI: 0.704 (any grade); 0.711 (high grade)
- Both models saved 29.6% of biopsies at a cost of missing 10% of higher grade tumors (at 10% 4K result or 39 PHI cut-off)
- Both models showed limited benefit on decision curve analysis

Prostate Cancer Treatment Options

Treatment Options

Depend upon...

• Stage of disease
• Patient’s age and health
• Patient’s personal preference
Treatment Options (Early Diagnosis)

- Watchful waiting or active surveillance
- External beam radiation therapy (EBRT) includes IMRT
- Brachytherapy (radioactive seeds)
- Cryosurgery (freezing prostate)
- Surgery (radical prostatectomy)
  - Open surgery
  - Conventional laparoscopic surgery
  - da Vinci Prostatectomy (robotic-assisted laparoscopic surgery)

Goals of Radical Prostatectomy

- Remove the prostate and cancer
- Preserve urinary function
- Preserve erectile function
- Analyze the prostate after surgery to assess risk of recurrence of cancer
Surgery: Gold Standard Treatment for Localized Prostate Cancer

"Because the entire prostate gland is removed with radical prostatectomy, the major potential benefit of this procedure is a cancer cure in patients in whom the prostate cancer is truly localized."

--(2007 AUA clinical guidelines)

Benefits of Surgery

• Up to 35% of tumors can actually be more aggressive than the pre-surgery assessment and biopsy results indicated

• Choosing surgery can:
  • Enable easier detection of cancer recurrence through PSA monitoring after a radical prostatectomy than after radiation therapy
  • Preserve your treatment options if there is a recurrence
Long-Term Survival and Localized Prostate Cancer

A study of 3,159 patients found that 15 years after treatment, those who had undergone radical prostatectomy had a 40% lower risk of death from prostate cancer than radiation patients.6

Surgery: Longer Survival vs. Any Other Treatment
**Nerve-Sparing Prostatectomy**

- Preserve nerves responsible for erections
- Nerves run alongside prostate
- *da Vinci* System permits surgeon to spare nerves
  - Enhanced magnification
  - Three-dimensional view
  - Robotically enabled *EndoWrist*® instruments

**Robotic-Assisted Surgery Access**

- **Open Surgical Incision**
- *da Vinci*™ Prostatectomy Incision
How can we overcome the drawbacks of laparoscopy?

- Provide a high-resolution 3D image
- Insert a computer between the surgeon’s hand and the instrument tip
- Increase the surgeon’s dexterity for the difficult aspects of the procedure, e.g.
  - Sparing the nerves to preserve erectile function
  - Preserving continence
  - Preserving quality of life

Clinical Concerns for Prostatectomy

“The Big 3”

1. Cancer Control – Margins
2. Urinary Control – Continence
3. Sexual Function – Potency
Conclusions

• Prostate Cancer diagnosis is controversial

• Patient selection is critical

• The answers point to more questions